REMARKS

Claims 1-7, 35-40, and 42 are pending in the application and all are rejected. Claims 1 and 35 are amended and claims 4, 40, and 41 are cancelled herein all without prejudice and without acquiescence. New claims 43-50 are added herein, and support for the new claims is found in the original claims and in at least paragraphs **[0268]** and **[0273]** of the specification. Thus, no new matter is entered herein.

Clarification of Issues

The Examiner notes in the Office Action on Page 2 that she would like to reinstate that the election of one SEQ ID NO: of a periaxin polynucleotide is not a species election but is an "election of a restricted SEQ ID NO: corresponding to an elected group." Applicants respectfully but strongly disagree with the Examiner, as the group is in fact a genus of periaxin polynucleotides comprising specific members that are different regions and/or fragments of periaxin polynucleotides, many of which overlap. To select one member of the group of periaxin polynucleotides is to select a specific sequence member of a genus of periaxin polynucleotides. Therefore, Applicants respectfully request that the Examiner reinstate that the election of one periaxin SEQ ID NO: is in fact a species election.

The Examiner states in the Office Action that claim 2 is withdrawn from consideration since it is dependent on non-elected species. However, in the previous Action Applicants amended this claim to be directed to SEQ ID NO:76, which is the elected species. Therefore, Applicants consider claim 2 not to be withdrawn but to be currently pending. Applicants respectfully request acknowledgement and clarification regarding this issue from the Examiner.

Applicants also request clarification of the Examiner's withdrawal of claim 6, as these sequences concern primers and not periaxin polynucleotides. That is, the sequences listed in claim 6 are not at all within the same group of sequences for the elected species of SEQ ID NO:76. Applicants respectfully request acknowledgement regarding this issue from the Examiner.

The Examiner objects to the specification because it contains an embedded hyperlink. Applicants amend the specification herein.

Clarification of Oath/Declaration Objection

The Examiner also objects to the disclosure and asserts that the Oath/Declaration is defective for not claiming priority and in not identifying the mailing or post office address of each inventor. Applicants kindly note the Examiner is in error and submits herewith both the originally filed unexecuted oath and Application Data Sheet (ADS) filed with the application and the executed Oath and Supplemental ADS sheets that contain the information in question. Applicants note that the mailing address is provided in the ADS, as is allowed pursuant to 37 C.F.R. §1.63(c), 37 C.F.R. §1.76, and MPEP §601.05.

Issues under 35 U.S.C. §112, paragraph 1

Claims 1-7, 35-40, and 42 are rejected under 35 U.S.C. §112, paragraph 1 for allegedly failing to comply with the enablement requirement. Applicants respectfully disagree.

In the outstanding Office Action, the Examiner delineates the arguments pursuant to the enablement requirements set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants respond accordingly.

Nature of the Invention

Independent and representative claim 1 is directed to a method of diagnosing myelinopathy in an individual by assaying a sample containing a periaxin nucleic acid for an alteration in the nucleic acid, wherein the alteration associates from the myelinopathy and wherein the myelinopathy is selected from the group consisting of Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS).

Independent and representative claim 35 regards a method of detecting the presence or absence of a mutation associated with a myelinopathy by isolating a periaxin test nucleic acid from a subject, comparing the test periaxin nucleic acid to a reference wild-type periaxin polynucleotide, and determining the differences between the test nucleic acid and the reference wild-type periaxin polynucleotide, wherein the differences are mutations in the periaxin polynucleotide of the subject, wherein the presence of a mutation in the periaxin polynucleotide of the subject is associated with the myelinopathy in the subject, and wherein

the myelinopathy is selected from the group consisting of Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS).

New claims 43-48 are directed to assaying *PRX* for mutations associated with a myelinopathy having a prominent sensory neuropathy. As discussed in Example 8, particularly paragraphs **[0268]** and **[0273]** (providing support for these claims), patients with *PRX* mutations present with marked sensory involvement, which is in contrast to patients having mutations in other CMT-associated genes, such as PMP22, MPZ, and so forth. Therefore, Applicants have shown that the prominent sensory neuropathy associated with periaxin mutations is well within the scope of these claims.

New claims 49-50 are directed to a method of detecting a polymorphism or mutation in a periaxin polynucleotide of an individual by obtaining a sample comprising the periaxin polynucleotide from the individual and assaying the periaxin polynucleotide for a polymorphism or mutation. Support for these claims is in Example 3 at paragraphs **[0244]** to **[0246]**.

Amount of Direction and Guidance

The Examiner asserts that the specification,

> "has not established that a statistically significant association exists between all of the specific mutations disclosed in the specification, and any myelinopathy, or any specific myelinopathy, or that a predictable correlation can be made as to an association between any mutation in the periaxin gene and any myelinopathy or any specific myelinopathy."

Applicants assert that a statistically significant association is not the proper standard for determining patentability so long as a reasonable association is determined. Applicants assert that an association does in fact exist between the *PRX* mutations and myelinopathies (see, for example, paragraph **[0009]** and the Examples). Although the Examiner alleges that Applicants have not established that a statistically significant association exists between all of the specific mutations disclosed in the specification, and any myelinopathy, or any specific myelinopathy, Applicants assert that the association is that a periaxin mutation exists with a

myelinopathy. Again, it is not required that *statistically significant* association exists, only that a reasonable one does exist. Applicants show that a variety of mutations in periaxin, including 2145T>A, 1102C>T, 2289delT, 2787delC, 2857C>T, or 247ΔC, associate with a myelinopathy, the exemplary embodiment being recessive Dejerine-Sottas neuropathy.

The Examiner also alleges that the specification has not established a predictable correlation between any mutation in the periaxin gene and any myelinopathy or any specific myelinopathy. The predictable correlation is that the defect in a periaxin polynucleotide is associated with a myelinopathy, and myelinopathies are each units of a spectrum of closely related diseases. Applicants are not trying to claim periaxin for a wide range of diseases but those as part of a phenotypically narrow range of myelinopathies. The specification states in paragraph **[0263]**: "The association of mutations in *PRX* with peripheral neuropathy not only identifies another genetic cause for the *CMT1 spectrum of myelinopathies* but also provides further insights into the molecular mechanisms *for these diseases*." (emphasis added)

The specification teaches in paragraph **[0004]** that myelinopathies such as Dejerine-Sottas neuropathy (DSN) and Charcot-Marie-Tooth disease type 1 (CMT1) are part of a spectrum of neuropathy phenotypes having different degrees of severity. Applicants assert that although at least fifteen genetic loci and six genes have been associated with this spectrum of disorders, this does not preclude a single gene such as periaxin from having a mutation in all of the disorders. In fact, there is a precedent for there being more than one defective gene even within the family itself, given that for CMT1, mutations in addition to PMP22 include those in MPZ, Cx32, EGR1, MTMR2, NDRG1 (see paragraphs **[0079]** and **[0080]**). Furthermore, DSS and CHN can be caused by mutations in multiple genes (MPZ and EGR2 for both), and the specification even states (paragraph **[0080]**): "...these myelinopathies appear to represent a *spectrum of related disorders resulting from myelin dysfunction*", given that each of the "genes are expressed in myelinating Schwann cells so that mutations probably exert their effects on Schwann cells." (emphasis added)

The specification notes in paragraph **[0005]** that Gillespie *et al.* (2000) associated periaxin with myelin sheath, so a skilled artisan would recognize that it is not undue to demonstrate mutations in different myelinopathies by assaying a periaxin polynucleotide.

This is in keeping with Applicants' paragraph **[0042]**, which clarifies that myelinopathy is defined as:

> "a defect in myelin, a lipid substance which forms a sheath around nerve fibers. The defect may be absence of myelin, loss of myelin, or faulty myelin. **In specific embodiments, the myelinopathy results in Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and/or Roussy-Levy Syndrome.** A skilled artisan is aware myelin is also referred to as a white substance representing membrane extensions of Schwann cells which ensheathe the peripheral nerve axon. Peripheral nerve myelinopathy refers to myelin of the peripheral nerve." (emphasis added)

In paragraph **[0007]** the specification teaches diagnosing myelinopathy by assaying periaxin, and specific myelinopathies are listed, such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS).

Thus, Applicants assert that a sufficient amount of direction and guidance are provided in the specification at the time of filing.

In contrast to the assessment in the Action, the present disclosure completely complies with the requirements of M.P.E.P. § 2164.03 and *In re Dreshfield* by first providing direction and guidance regarding a large number of operative species of periaxin polynucleotides (paragraph **[0064]**), means to obtain them (paragraphs **[0063]** and **[0236]-[0241]**), means to assay them for a mutation (paragraph **[0244]**), and the myelinopathies from which to screen (paragraphs **[0073]-[0083]**).

Applicants assert that if, for example, there was a case of an individual with CHN that did not have a periaxin mutation, this should not preclude Applicants from obtaining a patent on methods of diagnosing myelinopathies by identifying an associated periaxin mutation. In claim 1, for example, Applicants are not claiming that <u>all</u> cases of myelinopathies are caused by mutations in periaxin but instead that the presence of a mutation in periaxin is associated with a myelinopathy that is Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy

with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), or Roussy-Levy syndrome (RLS). Furthermore, Applicants remind the Examiner that claims directed to inoperable embodiments are not prohibited by the statutes. The Federal Circuit has explained that the fact that claims may encompass inoperative embodiments does not necessarily render them non-enabled, or invalid. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984). It is not the function of the claims to exclude possible inoperative substances. *Atlas Powder*, 224 U.S.P.Q. at 414.

Thus, Applicants respectfully assert that the amount of direction and guidance provided by the specification is commensurate with the scope of the claims. The standards set by the Examiner of statistically significant are unnecessarily high and improper.

Presence and Absence of Working Examples

The Examiner states beginning on page 5 of the Action:

> Although the specification does not demonstrate such, the specification asserts that the mutations could be associated with loss of function of the periaxin polypeptide. It is noted, however, that these examples also establish that the mere presence of a mutation (i.e., only a single copy) is NOT associated with the disease as in HOU579 family, where the unaffected parents had a single mutant polynucleotide and a wild type polynucleotide. Further there is no description of the type of peripheral neuropathy of the affected patients. (see page 65, example 3).

Applicants assert that the specification teaches that in some embodiments the association between a periaxin mutation and a myelinopathy reflects recessive inheritence, as indicated in paragraphs **[0242]** and **[0244]**. As stated in paragraph **[0244]**: "Families HOU418, HOU579 and HOU297 exhibit autosomal recessive inheritance." Therefore, although family members of HOU579 may comprise only one alteration in the *PRX* allele, this is because "...the unaffected parents and son of family HOU579 are each heterozygous carriers of a *PRX* mutant allele". The affected diseased member of the HOU579 family "is compound heterozygous for deletion 2289ΔT and a 1102C>T transition causing the nonsense mutation R368X", so this member comprises two defective *PRX* alleles consistent with the recessive nature of the disease.

In the telephonic interview of November 14, 2003, the Examiner expressed concern that the scope of the claims was not enabled because different inheritence patterns for myelinopathies, such as autosomal dominant, autosomal recessive, or X-linked inheritences would be covered. Applicants acknowledge that any type of inheritance pattern would, in fact, be covered by these claims because the claims concern myelinopathies having a periaxin defect, and the inheritance pattern is completely irrelevant. As stated in the accompanying affidavit of Dr. Jim Lupski, it is well-known in the field how to identify inheritance patterns based on tracking mutations in a family with an affected individual.

The Examiner also states in the Action on Page 6:

> Further examples in the specification merely assert correlation between mutations in *PRX* with myelinopathies in general, however no specific mutation is associated with any of the different types of myelinopathies as exemplified by the example 8 in the specification (see page 72).

However, paragraphs **[0264]** and **[0268]** clearly states that the mutations 2145T>A and 247ΔC are associated with peripheral neuropathy that identifies another genetic cause for the CMT1 spectrum of myelinopathies

Finally, regarding Table 2, the Action states on Page 6 that "....table-2 shows that the unaffected control subjects contain mutations in periaxin. The specification does not teach whether the mutations in table-2 are associated with loss of function or if they are statistically associated with any specific peripheral neuropathy or any specific myelinopathy."

The specification states in paragraph **[0246]**:

> Other *PRX* sequence variants identified in patients and controls are shown in Table 2. In specific embodiments, these represent benign polymorphic variants. In one specific embodiment the alleles identified in only one control chromosome represent rare polymorphisms, or in an alternative embodiment a recessive carrier state.

Table 2 is entitled "Alterations occurring in North American control chromosomes or unaffected family members," and Applicants assert that there are plenty of working examples in the specification to assist one of skill in the art how to identify these alterations as disease-causing in the diagnosis of specific myelinopathies.

Applicants assert that there are more than sufficient number and content of working examples provided in the specification to support association of *PRX* mutations with a range of myelinopathies within the CMT1 category, which is further supplemented by examples in the art (Boerkoel et al., 2001 (related to the instant specification); Guilbot et al., 2001; Delague et al., 2000; provided in a Supplemental Information Disclosure Statement filed herewith). Applicants teach in paragraph **[0062]** and **[0268]** that mutations in periaxin cause human peripheral myelinopathies, given that multiple unrelated DSN patients with recessive *PRX* mutations were identified as well as families associated with the spectrum of *PRX*-associated peripheral neuropathies. Applicants also provide a variety of means to obtain sequence information (paragraph **[0063]**) and a voluminous number of periaxin polynucleotide sequences (paragraph **[0064]**) to assay for mutations in an analysis.

Moreover, the specification in paragraphs **[0074]** through **[0083]** discuss different exemplary embodiments of myelinopathies having similar and overlapping phenotypes directed to at least defects in myelin, but also onion bulb defects (found in CMT1, DSS, and CHN); slowed motor nerve condution velocities (NCV) (found in CMT1, HNPP, DSS, and CHN); muscle weakness (CMT1 and CHN); gait disturbance or ataxia (CMT1 and RLS); and areflexia (CHN and RLS), for example. This is clear evidence that this is a ***group of highly related diseases having significant phenotypical overlap*** likely associated with a common *PRX* defect, in some embodiments.

In Example 1 (paragraphs **[0235]** to **[0241]**, Applicants provide materials and methods to practice exemplary embodiments of the invention, including obtaining the periaxin polynucleotide, mapping it, and screening for mutations, such as by PCR. Example 2 provides characterization of the *PRX* gene, including a tissue expression profile, *in situ* hybridization by FISH, and sequencing. Example 3 provides teaching of *PRX* mutation analysis in 168 peripheral neuropathy patients who had tested negative for mutations in *PMP22, MPZ, GJB1, EGR2*, or *MTMR2*. Even though alterations in *PRX* are described for unaffected family members, it is well-known in the field how to correlate a particular mutation with a disease.

Furthermore, Example 8 shows that *PRX* mutations are related to a spectrum of demyelinating neuropathies (in paragraph **[0268]**): "These two families confirm that putative

loss-of-function mutations in *PRX* cause autosomal recessive neuropathies and ***broaden the spectrum of PRX-associated peripheral neuropathies***." (emphasis added) Also (in paragraph **[0273]**): "Similar to the spectrum of phenotypes observed with mutation of other genes associated with CMT and related inherited peripheral neuropathies, the clinical phenotypes manifested in patients with mutations in *PRX* include CMT myelinopathies and DSN."

Applicants assert that even if one could argue that the specification did not provide enough working examples, Applicants submit that examples may be either "working" or "prophetic", and compliance with the requirements for enablement under 35 U.S.C. 112 does not require that an example is disclosed, or that the invention be reduced to practice prior to filing, *Gould* v. *Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) and M.P.E.P. 2164.02. Applicants, however, strongly assert that the present Examples do comply with 35 U.S.C. §112 and the invention was reduced to practice prior to filing of the priority document.

Furthermore, the Federal Circuit has held that § 112 does not require that the applicant describe exactly the subject matter claimed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Moreover, it is not necessary that a patent applicant test all the embodiments of his invention. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Section 112 requires simply that the patent applicant provide a disclosure which sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213. The identification of exemplary mutations associated within the spectrum of myelinopathies provides a disclosure that more than sufficiently enables the scope for myelinopathies, particularly given that the ability to associate mutations with particular diseases is achieved by well-known means in the art.

Level of Predictability and Unpredictability in the Art

The Examiner states in the Action on Page 7:

> "...the art does not establish a predictable association that any specific mutation in periaxin or any other genes is predictably

> associated with all of the large number of diseases encompassed by the recitation of 'myelinopathy'"

Applicants have provided multiple mutations in the specification that clearly relate to DSN and a spectrum of demyelinating neuropathies, and others in the art (Guilbot et al., 2001) have identified at least one other mutation in *PRX* associated with CMT4F. Therefore, it is reasonably predictable that other mutations in *PRX* will result in myelinopathic diseases.

The Examiner also reiterates that a statistically significant association has not been demonstrated with any of the disclosed *PRX* mutations and myelinopathy, and that there is no predictable correlation between the *PRX* mutations and myelinopathies. Applicants reiterate that a statistically significant correlation is not the standard for patentability, so long as a reasonable correlation exists. Furthermore, Applicants assert that given that multiple *PRX* mutations are provided in the specification and are known in the art for myelinopathies having highly related pathologies, there is most definitely a predictable correlation between *PRX* mutations and myelinopathies.

The Action also states on Page 7:

> "...to date, no teaching is available in the art with regards to a universal correlation between any mutation in periaxin and an association with any general or specific type of myelinopathy. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with any particular type of myelinopathy. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of any particular mutation in periaxin with any particular type of myelinopathy."

Applicants assert that they are not required to show a "universal correlation" between every possible *PRX* mutation and every type of myelinopathy. Applicants are only required to show a reasonable correlation, and in providing a variety of mutations associated within a spectrum of myelinopathies, Applicants assert that they are doing exactly what is required. Therefore, the scope of the present claims is commensurate with Applicants' teaching, and there is minimal unpredictability related to this technology.

The Examiner also alleges that the specification does not identify a critical nucleotide or amino acid alteration associated with loss of function or associated with myelinopathy.

Applicants assert that critical nucleotides or amino acid alterations are not required to be identified for patentability of the pending diagnosis claims. It is not unpredictable for a skilled artisan to be able to determine whether or not a particular sequence variation is associated with a disease state, and furthermore, it is routine to do so. In fact, even within the CMT family itself a variety of mutations in other genes have been associated with the disease (see paragraph **[0004]**).

In discussing claim breadth, M.P.E.P. § 2164.03 provides that:

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

M.P.E.P. § 2164.03, 2100-116 (1995). Should the Examiner feel that the present invention is directed to an art where certain results may be associated with a degree of unpredictability, M.P.E.P. § 2164.03 also supports Applicants' position on enablement rather than that advanced in the Action. M.P.E.P. § 2164.03 further provides:

> It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.
>
> *Id.* (quoting *In re Dreshfield*, 45 U.S.P.Q. 36 (C.C.P.A. 1940)).

Applicants assert that they have provided ***both*** sufficient numbers of *PRX* mutations and associating myelinopathies and appropriate language enabling the invention. Although some experimentation may be involved, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The correlation between particular mutations and disease states is performed by well-known means in the art, and the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in

the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants assert that the minor amount of experimentation to determine if an unknown periaxin mutation associates with a myelinopathy selected from Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS) raises very little unpredictability. This is particularly true given that patients from four unrelated demyelinating neuropathy families, three manifesting DSN and one with a severe demyelinating CMT, CMT4F, have recessive *PRX* nonsense and frameshift mutations (Boerkoel et al., 2001 (related to the instant specification); Guilbot et al., 2001; Delague et al., 2000).

Quantity of Experimentation Necessary

The Examiner alleges that a large amount of experimentation would be necessary to practice the invention as claimed, given the supposed lack of guidance in the specification and unpredictability in the art (addressed above). Applicants assert that there is more than sufficient evidence guiding one of skill in the art how to practice the invention by, at the very least, providing guidance of which polynucleotide to assay for a specific myelinopathy and how to do so.

Section 112 simply requires that there be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the relevant art how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). In *Angstadt*, the predecessor court to the Federal Circuit found that disclosure of many operable embodiments and one inoperative embodiment did not render a claim broader than the enabled scope because determination of the operable embodiments did not involve undue experimentation. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). Though some characterization of mutations may fall within the scope of the claims, one skilled in the art would be directed by disclosures in the Specification to do

so. With these disclosures, one skilled in the art could determine operable embodiments of the invention without undue experimentation.

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cirl 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). The scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants assert that a reasonable correlation certainly does exist, given that *PRX* shown w/DSS and the highly related myelinopathies such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS), are within the scope of reasonable correlation, particularly given their phenotypic similarities.

Applicants note that actual reduction to practice prior to filing is not required to prove enablement. *In re Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). Furthermore, it is well-settled case law that a specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). No undue experimentation is required to make and use the invention as claimed, given that Applicants provide detailed characteristics of exemplary mutations associated with DSN and related myelinopathies (see at least Example 8).

Even if experiments are necessary, a considerable amount of routine experimentation is permissible, especially where the Applicants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). The Office Action asserts that such experimentation is not routine, yet that argument fails to apply a standard of reasonableness to the state of the art and the relative skill of those in the art. It is well recognized "that the skill in the art of molecular biology is quite high." Id. at 548.

Furthermore, time is not a sole criterion of what constitutes undue experimentation in a particular case. Therefore, in contrast to the Examiner's assertions, the experimentation is, in fact, routine.

Moreover, although the Examiner states that many further experiments and hundreds of patient samples would be required to enable the invention, Applicants assert that even if this is true, time-consuming experiments are acceptable if the type of experimentation is standard in the art. An extended period of experimentation may be not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Yet further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands,* 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985). Techniques in molecular biology are, and were at the time of the application, well known and understood in the art.

There is simply no way that the undue experimentation standard can be used to maintain the present rejection. In assessing the question of whether undue experimentation would be required, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra; Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 U.S.P.Q. 2d 1016 (Fed. Cir. 1991). Given that Applicants utilize standard means of associating particular nucleotide alterations with a specific myelinopathy, Applicants state that the experimentation for associating these and/or other nucleotide alterations with other myelinopathies within this same highly related group of afflictions would be routine and not undue.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

A Petition for Extension of Time of Two Months and the requisite fee are filed herewith. Applicant believes no other fees are due with this response, other than the requisite fee for filing the Supplemental Information Disclosure Statement and for the Extension of Time fees. However, if another fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02086US1 from which the undersigned is authorized to draw.

Dated: December 18, 2003

Respectfully submitted,

By Melissa L. Sistrunk

Melissa L. Sistrunk
Registration No.: 45,579
FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
(713) 651-5151
(713) 651-5246 (Fax)
Agent for Applicant